Department of Obstetrics, Gynecology and Reproductive Sciences
Fax Number: 732-235-7318

ROBERT WOOD JOHNSON
UNIVERSITY MEDICAL GROUP
UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

Patient Appointments:
732-235-7301/02

University of Medicine and Dentistry of New Jersey

David B. Seifer, M.D.
Professor
Division Director

Ekkehard Kemmann, M.D.
Professor

Robert Shelden, Ph.D.
Associate Professor
Director, Laboratory Services

Date: 3/3/2004

Dockets Management Branch,
Food and Drug Administration,
Room 1061,
5630 Fishers Lane, Rockville, MD 20852.

Petition to Remove Category X Categorization for Estradiol in Use-in-Pregnancy Labeling

Dear Sir/Madam:

In the most recent publication of the PDR I noted that the FDA indicates that estradiol is a category X substance in the Use-in-Pregnancy Section. I believe that this categorization is inappropriate.

It is my understanding that until recently progesterone had also been listed as a category X substance. Progesterone has been moved to category B. I am at loss to explain to the students and residents I teach why estradiol would be in category X. There is sufficient evidence indicating that estradiol should not be in that category.

1. Estradiol is normally present during pregnancy. Indeed, there is massive production of estrogens during pregnancy by the fetal-placental unit. According to Speroff, " a rise in estradiol begins in weeks 6-8 when placental function becomes apparent" (1) "During pregnancy ... estradiol excretion is increased about 100 times over nonpregnant levels." (1) It would be hard to understand that a substance present in large amounts during pregnancy is a teratogen.
2. Estrogens may be necessary during pregnancy. Blocking estrogen synthesis by the use of an aromatase inhibitor during pregnancy of primates led to a significant increase in miscarriages (2).
3. Low estrogen levels during pregnancy may indicate fetal problems. Clinicians routinely use measurements of estriol in the assessment of fetal well being.

2004P-0122

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4. Exogenous estradiol administration is routinely used by physicians during early pregnancy in the context of assisted reproduction. Estradiol, typically at a dose of 4-8mg, is used in to women who receive embryos obtained as a result of ovum donation in IVF. Estradiol along with progesterone is given not only during the luteal phase but also during early pregnancy to maintain uterine support until week 8-10 when the placenta takes over the hormonal support. (3)
5. There is no evidence that exogenous use of estradiol has been linked to malformations.

It appears to me that progesterone had been in category X because at that time progestins were viewed as a singularity, and, apparently, this approach is still taken in regard to estrogens. Certainly specific estrogens are well recognized as teratogens (DES comes immediately to mind) and studies have also linked steroids used in OCPs with births defects. (4) However, it may be useful for a number of reasons to take a more differentiated view with estrogens.

1. A differentiated view reflects the scientific evidence. Dealing with estrogens as a singularity is overly simplistic.
2. The FDA position should be in agreement with the scientific evidence.
3. Estradiol has an indicated use in certain clinical situations during pregnancy.
4. Patients who require estradiol during pregnancy are placed in an impossible situation, - they are told that they need the medication for the benefit of the pregnancy/baby and also told that this medication is harmful to the baby. This leads to anxiety, distrust, and confusion and may initiate unnecessary and costly testing to assure that the baby is normal. Thus, the current listing of estradiol may be harmful.

I like to petition the FDA to review the standing of estradiol in the context of Use-in-Pregnancy labeling.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Thank you

Dr. B. Kemmann

CC: American Society of Reproductive Medicine
1209 Montgomery Highway
Birmingham, AL 35216-2809

References

1. Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. Sixth Edition. Baltimore: Lippincott Williams & Wilkins, 1999. Page 282.
2. Albrecht ED, Aberdeen GW, Pepe GJ. The role of estrogen in the maintenance of primate pregnancy. Am J Obstet Gynecol 2000;182:432-8.
3. Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. Sixth Edition. Baltimore: Lippincott Williams & Wilkins, 1999. Page 1144.
4. Lammer EJ, Cordero JF. Exogenous sex hormone exposure and the risk for major malformations. JAMA 1986;255:3128-32.

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5630 Fishers Lane, Rockville, MD 20852.

Fax: (301) 827 6870

Addendum to:
Petition to Remove Category X Categorization for Estradiol in Use-in-Pregnancy Labeling

Dear Sir/Madam:

To the best of my knowledge, a reclassification of Estradiol, currently in the Use-in-Pregnancy X Category, would not have a significant environmental impact.

Sincerely,

Dr. E. Kemmann

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